IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	UCKUN	Examiner:	R. TRAVERS
Serial No.:	09/272,821	Group Art Unit:	1617
Filed:	MARCH 20, 1999	Docket:	12152.55US01
Confirmation No.:	6130		
Due Date:	DECEMBER 1, 2003		
Title:	NNI FOR TREATMENT OF MULTI-DRUG RESISTANT HIV		

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By: Patricia Cygan
Name: Patricia Cygan

Mail Stop Appeal Brief-Patents
Commissioner for Patents
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23552
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By: Patricia Cygan
Name: Patricia Cygan

APPELLANT'S BRIEF ON APPEAL

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Brief is presented in support of the Appeal filed October 1, 2003, from the final rejection of Claims 23-44 of the above-identified application, as set forth in the Office Action mailed July 1, 2003.

A check for $165.00 to cover the required fee for filing this Brief is enclosed. An original and two copies of the Brief are enclosed herewith.

I. REAL PARTY OF INTEREST

The Real Party of Interest is Parker Hughes Institute.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences for the above-referenced patent application.

III. STATUS OF CLAIMS

Claims 23-44 are pending and are the subject of this Appeal (Appendix 1, Claims).

IV. STATUS OF AMENDMENTS

An Amendment in response to the final Office Action was filed on August 26, 2003, under 37 C.F.R. § 1.116. By way of Advisory Action mailed October 2, 2003, this response was not entered and deemed not to place the application in condition for allowance.

V. SUMMARY OF THE INVENTION

Briefly, Appellants' invention is finding two particular non-nucleoside inhibitors (NNI) of HIV reverse transcriptase that have shown particular efficacy against multiple strains of HIV, including mutant strains. These two compounds are identified as DDE236 and DDE240 (page 4, line 11 of the specification) and structural formulas for these two compounds are shown also on page 4 of the specification.

Prior to Appellant's invention, conventional HIV agents were known, many suffering from toxicity problems, lack of bioavailability or short lived *in vivo*, having viral resistance, or combinations thereof. (Lind et al, page 3, lines 21-24.) Lind et al. provides millions of compounds generically and names thousands of compounds in its specification. In addition, Lind et al. made over 400 compounds by way of examples and illustrated HIV activity for many of its compounds. Lind et al. do not address efficacy against resistant strains of HIV for any of its compounds.

Advantageously, Appellant's invention provides two specific thiourea compounds which were not made or tested in Lind et al., but generically covered by Lind et al.'s claims and

disclosed by name in the Lind et al. specification. Appellant has found surprising activity for these two compounds against mutant strains of HIV and provide very surprising efficacy against resistant strains of HIV superior to Lind et al.'s most preferred compound. (Data at page 12, Table 2 of Appellant's specification.)

VI. ISSUES PRESENTED FOR REVIEW

1. Whether the specification and claims 23, 25, 26, 29, 30, 31, 34, 35, 36, 39, 41 and 42 are non-enabling under 35 U.S.C. § 112, first paragraph.

2. Whether claims 23, 25, 26, 29, 30, 31, 34, 35, 36, 39, 41 and 42 are indefinite under 35 U.S.C. § 112, second paragraph.

3. Whether claims 23-44 are unpatentable under 35 U.S.C. § 103 over Lind et al., WO 93/03022.

VII. GROUPING OF CLAIMS

For purposes of the § 112 rejections, the claims should be divided among:

Group 1: Claims 23, 29, 34 and 39.

Group 2: Claims 25, 26, 30, 31, 35, 36, 41 and 42.

For purposes of the rejection under 35 U.S.C. § 103, the following groups should be considered:

Group 1: Claims 23-44.

VIII. ARGUMENT

1. Rejection Under 35 U.S.C. § 112, First Paragraph

A. The Group 2 claims in this category, claims 25, 26, 30, 31,35, 36, 41 and 42, do not contain the term "resistant to a chemotherapeutic agent". Thus, the Examiner's rejection should not apply to these claims and the rejection should be reversed.

B. Group 1 claims 23, 29, 34 and 39 comply with the enablement requirement of 35 U.S.C. § 112, first paragraph. Also, in the alternative, all the rejected claims comply with the enablement requirement.

Claims 23, 25, 26, 29, 30, 31, 34, 35, 36, 39, 41 and 42 have been rejected under 35 USC § 112, first paragraph as allegedly lacking an enabling description.

The Examiner stated, "Applicant fails to set forth the criteria that allows the skilled artisan to identify those HIV strains 'resistant to a chemotherapeutic agent'. Additionally, Applicant fails to provide information allowing the skilled artisan to ascertain these compounds without undue experimentation." In addition the Examiner stated, "The instant claims read on all HIV strains 'resistant to chemotherapeutic agent', necessitating an exhaustive search for the embodiments suitable to practice the claimed invention."

A. The Test for Undue Experimentation

"The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 279 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied.[1]

"The test for what constitutes undue experimentation is not merely quantitive, since a considerable amount of experimentation is permissible, if it is merely routine. . ."[2] Further, a patent need not disclose what is well known in the art.[3]

As the Examiner indicated, the Federal Circuit in *In re Wands* set forth eight factors for considering whether a specification is enabling. The eight factors are:

1. The Quantity of Experimentation Necessary
2. The Amount of Direction or Guidance Provided

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[1] *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)." MPEP § 2164.01
[2] *In re Wands*, Id. at 737, 8 USPQ2d at 1404; *See also* MPEP § 2164.06
[3] *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984); See also MPEP § 2164.01

3. The Presence or Absence of Working Examples
4. The Nature of the Invention
5. The State of the Prior Art
6. The Relative Skill of Those in the Art
7. The Predictability of the Art
8. The Breadth of the Claims

B. Practice of the Invention as Claimed in Claims 23, 25, 26, 29, 30, 31, 34, 35, 36, 39, 41 and 42 Does Not Require Undue Experimentation

Nothing more than permissible routine testing as would be understood by one skilled in the art may be required to practice the invention as claimed invention

The identification of HIV strains resistant to a chemotherapeutic agent and of such chemotherapeutic agents is accomplished by standard techniques well known in the art. For example, one can monitor CD4 cell counts, immune complex-dissociated p24 antigen, viral phenotype, and viral load in plasma of a patient receiving an anti-HIV chemotherapeutic agent. See, *e.g.*, Rusconi et al., *Antivir. Ther.*, 1(4):211-219, Dec. 1996, at 211 (abstract). Such methods are well known and routine in the art. Further, the Examiner himself, in an Office Action dated September 21, 2001 (Paper No. 14) indicated an alternative and well-known way of identifying the presence of a resistant strain of HIV; namely, a physician could identify a patient harboring a resistant HIV strain by the mere fact that the patient is not responding to anti-HIV chemotherapy. *See* Paper No. 14 at p. 3. Identification of which chemotherapeutic agents a HIV virus is resistant to flows from the techniques described above and requires no additional testing. That is, identification of a resistant to a chemotherapeutic agent necessarily results in identification of a chemotherapeutic agent to which the virus is resistant, thus no additional testing is required.

Resistant HIV viruses can also be identified through well-known cell culture techniques, as indicated in the present specification. One can, *e.g.*, measure the concentration of a

chemotherapeutic agent required to inhibit replication of a sensitive HIV strain and compare that to the concentration required to inhibit replication of a different strain. If the different strain is less sensitive to the chemotherapeutic agent than the sensitive strain, the different strain is considered sensitive. See, *e.g.*, Table 2 at page 12 of the specification where HTLV IIIB is indicative of a sensitive strain and RT-MDR is indicative of a resistant strain.

Further, one can identify resistant HIV by determining whether the HIV contain a known mutation resulting in resistance to known chemotherapeutic agents. Such mutations are discussed at, for example, page 2, lines 1-4 of the present specification. These mutants are readily identified through well-known techniques, such as nucleotide sequencing. See, *e.g.*, Masquelier et al., *Antivir. Ther.*, 4(2): 69-77, 1999 (abstract).

The analysis of the *Wands* factors as applied to claims 23, 25, 26, 29, 30, 31, 34, 35, 36, 39, 41 and 42 of the present application is as follows:

1. The Quantity of Experimentation Necessary

As mere routine experimentation is required to practice the claimed invention commensurate with the scope of claims 23, 25, 26, 29, 30, 31, 34, 35, 36, 39, 41 and 42, the quantity of experimentation is not undue. Such a conclusion is required by, e.g., MPEP § 2164.06: "The test for what constitutes undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. . ." citing *In re Wands*.[4]

Some examples of routine experimentation resulting in identification of a strain of HIV resistant to a chemotherapeutic agent are discussed above. For example, mere monitoring of CD4 cell counts, immune complex-dissociated p24 antigen, viral phenotype, and viral load in plasma of a patient receiving an anti-HIV chemotherapeutic agent will allow one skilled in the art to determine whether a HIV virus is resistant to the anti-HIV chemotherapeutic agent. Such techniques are well known and a routine part of treatment of an HIV infection. In addition,

[4] 858 F.2d at 737, 8 USPQ2d at 1404

simply monitoring patient outcome can be an indicator of whether a patient is harboring a resistant strain of HIV. Further, routine cell culture experimentation, where the ability of a chemotherapeutic agent to inhibit HIV replication is compared between two or more cell lines infected with different strains of HIV, can be used to identify strains of HIV that are resistant to the chemotherapeutic agent. One skilled in the art can also identify resistant HIV by determining whether the HIV contain a known mutation resulting in resistance to known chemotherapeutic agents.

Appellant asserts that none of the above experimentation and well known techniques are complex. However, to the extent that they are determined by the Examiner to be complex, such a determination cannot result in a finding that such experimentation is undue because one of skill in the art typically engages in such experimentation:

> "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub. nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404."
>
> MPEP § 2164.01
>
> 2. The Amount of Direction or Guidance Provided

"A patent need not teach, and preferably omits, what is well known in the art."[5] As discussed above, one of skill in the art, through mere routine experimentation using well-known techniques, could readily identify which strains of HIV are resistant to a chemotherapeutic agent and those chemotherapeutic agents to which the HIV are resistant. As such techniques and experimentation are well known in the art, it is appropriate for the specification to omit a

[5] MPEP § 2164.01, citing *In re Buchner*, 929 F.2d 660,661, 18 USPQ2d. 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 91, 94 (Fed. Cir. 1986), *cert. denied*, 480 US 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984)

discussion of how to perform such experimentation using such techniques. One of skill in the art, upon reading the specification, would understand the distinction between sensitive and resistant strains of HIV and, based on knowledge already in their possession, would be able to identify those strains that are resistant to a chemotherapeutic agent.

3. The Presence or Absence of Working Examples

While neither 35 U.S.C. § 112, first paragraph, nor any of the other sections of the Patent Statute or Patent Rules require that a specific working example be disclosed, Appellant has provided working examples showing the effectiveness of the two compounds within the claimed method against several strains of HIV resistant to one or more chemotherapeutic agent. See, *e.g.*, Table 2 at page 12 of the specification. Disclosure of such working examples is clearly sufficient for purposes of enablement.

4. The Nature of the Invention

The nature of the claimed invention involves inhibition of replication of drug-resistant HIV with the two specific compounds within the claims. The two specific compounds lie at the heart of the invention, due to their increased efficacy, relative to known and approved anti-HIV chemotherapeutics. The identification of compounds having the properties associated with the two specific compounds is indeed a difficult task. However, as discussed above, how to identify resistant strains of HIV and agents against which the HIV are resistant, which the Examiner has indicated as lacking an enabling disclosure, are so well known in the art that Appellant is perplexed as to why the Examiner rejected the claims as lacking an enabling disclosure.

5. The State of the Prior Art

The principles underlying treating HIV infection and inhibiting HIV replication with non-nucleoside inhibitors of reverse transcriptase is well known. See, e.g., Shafer et al. "A guide to HIV-1 reverse transcriptase and protease sequencing for drug resistance studies" in *Human Retroviruses and AIDS,* Theoretical Biology and Biophysics. Los Alamos National Laboratories,

2001, pp. 1-51 (particularly pages 5-11). However, it is the identification of compounds useful against resistant strains of HIV that is difficult. Surprisingly, Appellant has identified two such compounds and methods of their use are claimed. Appellant has disclosed the inventive aspect of the claimed invention, namely identification of two compounds useful against drug-resistant HIV. The identification of resistant strains of HIV and agents against which the strains are resistant is known in the art and well within the ability of one of skill in the art.

6. The Relative Skill of Those in the Art

The level of skill in the art of resistant HIV was high at the time the present application was filed. For example, a PubMed database search for publications prior to March of 1993 resulted in 1561 publications related to "drug resistant HIV."

7. The Predictability of the Art

As indicated above, the difficulty in the resistant HIV art is in identifying compounds useful for treatment of resistant HIV and inhibition of HIV replication. Thus, Appellant's claims are limited to only two compounds shown by the instant specification to possess superior properties to known and approved anti-HIV compounds. The predictability of the art with regard to the ability to identify resistant HIV strains and the agents against which they are resistant is quite high. As indicated above, the techniques for such identification are well known and are quite accurate and predictable in their results.

8. The Breath of the Claims

The breadth of the claims at issue is quite narrow. The claims are directed to a method of inhibiting replication of drug-resistant HIV strains using only two specified compounds. The specification teaches the effectiveness of these two compounds in inhibiting replication of drug-resistant HIV and in doing so provides guidance for how to test the two compounds for effectiveness in inhibiting replication of drug-resistant HIV. As discussed above, the

identification of drug resistant strains of HIV and the chemotherapeutic agents to which they are resistant is well within the abilities of one skilled in the art .

C. Summary

Appellant asserts that the specification provides adequate guidance with regard to how to make and use the invention commensurate in scope with claims 23, 25, 26, 29, 30, 31, 34, 35, 36, 39, 41 and 42. These claims recite only two compounds, which the specification teaches as being effective for inhibiting replication of drug-resistant HIV. The specification teaches how to make and use the two compounds according to the claims at issue. However, the Examiner contends that the specification lacks an enabling disclosure for failing to set forth the criteria that allows the skilled artisan to identify those HIV strains resistant to a chemotherapeutic agent. As indicated above, one of skill in the art through routine, and well-known experimentation can readily ascertain whether a strain of HIV is resistant to a chemotherapeutic agent. In light of the specification and the level of skill in the art, Appellant respectfully asserts that a skilled artisan, upon reading the specification, could practice the invention commensurate in scope with the claims without undue experimentation.

In view of the above, the Examiner's rejection is in error and should be reversed.

Should the Board sustain the rejection, Appellant requests reversal of the rejection as to claims 25 and 26, and their respective dependent claims, claims 30, 31, 35, 36, 41, and 42, since these claims do not recite "resistant to a chemotherapeutic agent."

2. Rejection Under 35 USC § 112, Second Paragraph

Claims 23, 25, 26, 29, 30, 31, 34, 35, 36, 39, 41 and 42 have been rejected under 35 USC § 112, second paragraph as allegedly being indefinite.

The Examiner rejected claims 23, 25, 26, 29, 30, 31, 34, 35, 36, 39, 41 and 42 as being indefinite for reciting the phrase "resistant to a chemotherapeutic agent." The Examiner stated

that the phrase was indefinite because criteria for defining HIV strains resistant to a chemotherapeutic agent are not disclosed in the specification.

Appellant asserts that the phrase "resistant to chemotherapeutic agent" in the context of HIV resistant strains is clear and definite because such language is well-known and understood in the art. A search of the literature indicates at least 1561 journal articles discussing drug-resistant HIV were published prior to March 1993. In addition, what is meant by "resistant to chemotherapeutic agent" is discussed throughout the specification. For example, page 1, lines 24-29 discusses that mutations and selective pressure can result in drug resistant HIV strains, and page 2, lines 1-4 presents examples of known resistant strains. The phrase "resistant to chemotherapeutic agent" is well understood by those skilled in the art and adequately discussed in the specification, thus Appellant asserts that claims 23, 25, 26, 29, 30, 31, 34, 35, 36, 39, 41 and 42 are clear and definite.

Should the Board sustain the rejection, Appellant requests reversal as to claims 25 and 26, and their respective dependent claims, claims 30, 31, 35, 36, 41, and 42, for reciting "resistant to a chemotherapeutic agent" when the claims do not recite "resistant to a chemotherapeutic agent."

3. Claims 23-44 are Not Obvious Over Lind et al.

A. Obvious to Try is Not Obviousness Under 35 USC §103

The Examiner argues that it would be obvious, based on the teachings of Lind et al., to try to treat resistant HIV using the compounds recited in the present claims. However, "obvious to try" is not the same as "obviousness".[6]

The Examiner is, in essence, asserting that it would be obvious to go through the millions of compounds disclosed[7] by Lind et al. to reach one of the two compounds recited in the present

[6] *In re Goodwin*, 576 F.2d 375, 377 (CCPA 1978), aff'd, 599 F.2d 1061 (CCPA 1979)

[7] The claims in Lind et al. cover millions of compounds. Over fifty pages of Lind et al. recite a dictionary list of thousands of compounds. There are about 450 examples illustrated in Lind and biological data provided for most of the compounds made but not directed to resistant HIV.

claims.[8] Clearly, this would not be an acceptable approach for treating an AIDS patient not responding to conventional therapy.

The Examiner pointed to page 3, lines 20-24 of Lind et al. as providing motivation to use the compounds recited in the present claims against resistant strains of HIV. The area of the Lind patent publication to which the Examiner pointed reads as follows:

> Unfortunately, many of the compounds [useful for inhibiting HIV or treating AIDS] suffer from toxicity problems, lack of bioavailability or are short lived in vivo, viral resistance, or combinations thereof.[9]

Such a statement is hardly sufficient to provide one skilled in the art with motivation to use the two compounds recited in the present claims against resistant HIV when Lind et al. do not disclose any activity data for the two compounds and when Lind et al. disclose that the most structurally similar compound tested has inferior activity against non-resistant HIV.

Simply stated, nothing in Lind et al. suggests that the two compounds recited in the present claims would have the superior efficacy against resistant HIV as disclosed in Appellant's specification.

In this regard, the Examiner pointed to Example 4 on page 158 of Lind et al, where the "core" (as termed by the Examiner) compound of the compounds recited in the present claims is disclosed. However, the activity of this "core" compound in Example 4 of Lind et al. is considerably less than the activity of other compounds having a different core.[10] Reproduced below is an illustrative table summarizing the pertinent results from Lind et al.

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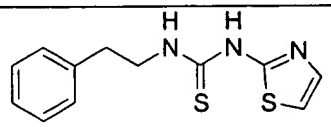
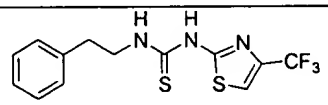
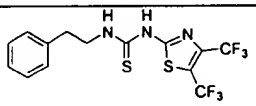
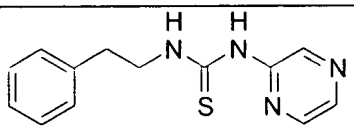
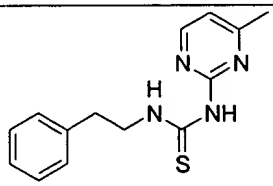
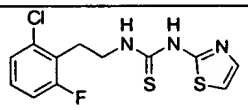
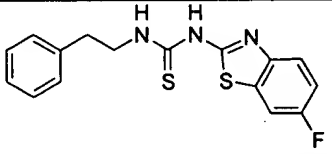
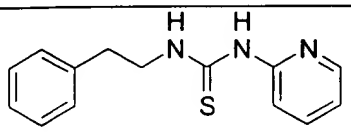
[8] The two compounds recited in the present method claims were not made nor tested for even conventional HIV activity by Lind et al.
[9] WO 93/03022 at page 3, lines 21-24
[10] see Tables A1-A3 at pages 128-142 of Lind et al.

Test Compound	% Inhibition of HIV-RT at below compound concentration			
	100 ug/ml	10 ug/ml	1 ug/ml	0.1 ug/ml
 1-Phenethyl-3-thiazol-2-yl-thiourea	-	100	100	2
 1-Phenethyl-3-(4-trifluoromethyl-thiazol-2-yl)-thiourea	66	24	100	-
 1-(4,5-Bis-trifluoromethyl-thiazol-2-yl)-3-phenethyl-thiourea	99	85	71	-
 1-Phenethyl-3-pyrazin-2-yl-thiourea	100	100	4	-
 1-(4-Methyl-pyrimidin-2-yl)-3-phenethyl-thiourea	100	64	42	-
 1-[2-(2-Chloro-6-fluoro-phenyl)-ethyl]-3-thiazol-2-yl-thiourea	100	100	100	-
 1-(6-Fluoro-benzothiazol-2-yl)-3-phenethyl-thiourea	100	100	100	-

Test Compound	% Inhibition of HIV-RT at below compound concentration			
	100 ug/ml	10 ug/ml	1 ug/ml	0.1 ug/ml
 1-Phenethyl-3-pyridin-2-yl-thiourea	6	2	0	-

As shown from the table above, the data disclosed in Lind et al. indicates that 1-Phenethyl-3-pyridin-2-yl-thiourea, the "core" of the compounds recited in the present claims, is considerably less effective than other compounds having different cores.

Appellant submits that a physician treating an AIDS patient not responding to conventional therapy would not select derivatives of a core compound having such low activity in comparison to the other compounds shown in Lind et al. Rather, one would be motivated to select the compounds disclosed in Lind et al. as having the best activity against non-resistant HIV, or structurally similar compounds.

A person of skill in the art, in attempting to treat or inhibit resistant HIV, would not, in light of Lind et al., logically arrive at either of the two compounds recited in the present claims for use in treating or inhibiting resistant HIV. While it may be obvious for a physician to select a different therapeutic compound when faced with a patient unresponsive to conventional therapy, there is nothing in Lind et al. that would direct or even suggest to a physician to try one of the two compounds recited in the present claims.

B. Lind et al. Do Not Suggest a Reasonable Expectation of Success

To establish obviousness under 35 USC 103, some reasonable expectation of success must be gleaned from the prior art.

> "Where claimed subject matter has been rejected as obvious ... a proper analysis under § 103 requires, inter alia, consideration of ... whether the prior

art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success."[11]

The Examiner failed to show that one would have any reasonable expectation of success, based on the disclosure of Lind et al., in using one of the two compounds recited in the present claims in inhibiting resistant HIV. As stated above, the "core" compound disclosed in Lind et al. was considerably less effective than other compounds in inhibiting non-resistant HIV. Lind et al. provide no suggestion that the compounds recited in the present claims would have superior properties against resistant HIV. In fact, Lind et al. do not discuss the efficacy of any of the millions of disclosed compounds against any resistant strain of HIV.

Resistant HIV strains are different from the non-resistant HIV disclosed in Lind et al. Resistant strains develop mechanisms, typically gene mutations, which render them resistant to the inhibitory effects of compounds. Often, HIV strains can develop resistance to many classes of inhibitory compounds. Such strains are termed multi-drug resistant HIV. Resistant HIV, because of their resistance mechanisms, are more difficult to treat than non-resistant strains. In fact, the main difficulty in HIV therapy is the rapid emergence of drug resistant strains of the virus.[12]

Lind et al. disclose non-resistant strains of HIV-1. These strains have not developed any resistance mechanisms and are relatively easy to treat. Lind et al. do not disclose resistant HIV strain, nor do they suggest that the compounds recited in the present claims would have superior properties against resistant HIV. Based on the difficulties of treating resistant HIV and the fact that Lind et al. teach that the "core" compound of the compounds recited in the present claims exhibit relatively low activity compared to other compounds having a different core, one would

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[11] *In re Vaeck* (1991), .947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); see also *In re Dow Chemical Co.*, 837 F.2d 469,473, 5 USPQ2d 1529, (Fed. Cir., 1988); *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d) 1016, (CAFC 1991)

[12] Tanuri et al., *Antimicrobial Agents and Chemotherapy*, 43(2): 253-358, 1999 at 253

have no expectation of success in using the two compounds recited in Appellant's claims for inhibiting resistant HIV.

C. Appellant Has Shown Unexpected Results

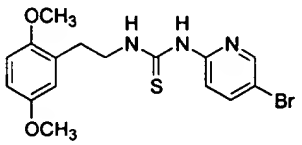
Nothing in Lind et al. suggests that either of the two compounds recited in the present claims would be effective against drug resistant HIV. As indicated above, drug resistant strains of HIV are more difficult to treat than non-resistant HIV. DDE236 and DDE240, which are the compounds recited in the present claims, are quite potent against various resistant HIV strains, as shown in Table 2 at page 12 of the specification of the present application. The fact that these compounds have such potency is quite surprising.

Further, nóthing in Lind et al. suggests that that the compounds recited in the present claims, which are non-nucleoside inhibitors (NNIs) of reverse transcriptase, would be effective against strains of HIV resistant to conventional NNIs. As shown in Table 2 at page 12 of Appellant's application, the compounds recited in the present claims (DDE236 and DDE 240) are effective against HIV resistant to conventional NNIs. For example, Nevirapine and Delavirdine, which are conventional NNIs, were shown to be substantially ineffective against strains of HIV having a mutation at amino acid 181 of reverse transcriptase. However, DDE236 and DDE240 were much more effective against such resistant HIV (see Table 2 at page 12 of the present specification). In addition, DDE236 and DDE240 were 80-1000 times more potent than Nevirapine and Delavirdine against the HIV multi-drug resistant strain, RT-MDR. These results are surprising and certainly unexpected. Relevant portions of Table 2 of Appellant's application are reproduced below.

RT Inhibitors	RRT (μM)	HTLV IIIB WT	RT-MDR (74V, 41L, 106A, 215Y)	A17 (Y181C)	A17 variant (Y181C, K103N)
		IC50 p24 (μM)	IC50 p24 (μM)	IC50 p24 (μM)	IC50 p24 (μM)
DDE236	0.1	<0.001	0.005	0.1	11
DDE240	0.6	<0.001	0.005	0.2	41
Delavirdine	1.5	0.009	0.4	50	>100
Nevirapine	23	0.034	5	>100	>100

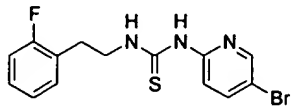
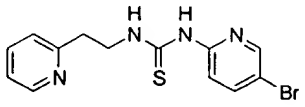
N.D.= not determined; WT=wild type.

Furthermore, Lind et al. at page 118, line 38-40 disclose Trovirdine [N-(2-pyridylethyl)-N'-(5-bromo-2-pyridyl)thiourea] as the single "especially preferred" compound.[13] Nothing in Lind et al. would point to the two structurally different[14] compounds in the present claims as having superior properties to Trovirdine. Surprisingly, however, Appellant has discovered that the two compounds recited in the claims 23-44, compounds having an "inferior" 1-phenethyl-3-pyridin-2-yl-thiourea "core" - are *more* effective than Trovirdine in inhibiting replication of drug resistant HIV. A relevant portion of Table 2 of Appellant's application is reproduced below. Structures were added here for illustration of the differences in chemistry.

RT Inhibitors	RRT (μM)	HTLV IIIB WT	RT-MDR (74V, 41L, 106A, 215Y)
		IC50 p24 (μM)	IC50 p24 (μM)
DDE236  [2-(2,5-dimethoxyphenylethyl)]-[2-(5-bromopyridyl)]-thiourea	0.1	<0.001	0.005

[13] From the millions of compounds covered in Lind et al.

[14] The two compounds have a substituted phenyl group on one end of the thiourea and a pyridyl group on the other; whereas Lind et al.'s single preferred compound has pyridyl groups on both ends of the thiourea.

DDE240  [2-(2-fluorophenylethyl)]-[2-(5-bromopyridyl)]-thiourea	0.6	<0.001	0.005
Trovirdine  2-pyridylethyl-(5-bromo-2-pyridyl)-thiourea	0.8	0.007	0.02

WT=wild type.

Clearly the fact that the two compounds recited in claims 23-44 are more efficacious than Trovirdine, the single "especially preferred" compound disclosed by Lind et al. provides surprising and unexpected results. This data from Appellant's specification is clear, convincing and commensurate in scope with the claims which are to methods of treating resistant HIV with two compounds.

D. The Examiner's Reliance on *In Re Swinehart* is Misplaced

The Examiner asserts that elucidation of the mode of action does not impart patentable moment to otherwise old and obvious subject matter, citing *In re Swinehart*.[15] However, *In re Swinehart* stands for the proposition that claims to compounds reciting previously unknown functional properties are not patentable over prior art disclosing the compound itself. However, Appellant is claiming a new use of a known compound, not a compound having functional properties. It is well-established patent law that new uses of old compounds are patentable. For example, 35 U.S.C. 100(b) defines "process" as including "a new use of a known ... composition of matter", while 35 U.S.C 101 explicitly states that "[w]hoever invents or discovers any new and useful process ... may obtain a patent therefor..." Accordingly, a new use of a known

[15] *In re Swinehart*, 439 F.2d 210; 169 USPQ 226 at 229 (CCPA 1971)

compound is patentable. The courts have also agreed that a new and unobvious use of a known composition is patentable.[16]

E. Appellant's Ultimate Utility is New and Unobvious

The Examiner asserted that the ultimate utility of the claimed invention is old and well known and described in the prior art. Apparently, the Examiner neither recognized the differences between drug-resistant HIV and the HIV disclosed in Lind et al., nor recognized the difficulties associated with treating or inhibiting drug-resistant HIV.

Appellant respectfully submits that the use of the compounds recited in the present claims to inhibit drug-resistant strains of HIV is new and non-obvious over the art cited by the Examiner. High replication rates of HIV unfortunately lead to genetic variants, which could result in drug resistance, especially when selective pressure is introduced in the form of drug treatment. In fact, the main difficulty with current treatment of HIV is the development of drug resistance of the virus.[17] Finding compounds useful for treating resistant HIV is no easy task. This is particularly true of compounds that exhibit improved ability to inhibit known drug resistant strains of HIV. Appellant has found that the two compounds recited in the present claims, DDE 236 and DDE 240, exhibit such improved ability. Nothing in the art cited by the Examiner (Lind et al.) teaches or suggests that DDE 236 and DDE 240 would have such properties.

In view thereof, the Examiner's rejection of the claims on the ground of obviousness over Lind et al. is erroneous both as to the facts and the law; its reversal is earnestly solicited.

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[16] *Rhom & Hass Co. v. Roberts Chemicals*, 245 F.2d 693, 113 USPQ 423 (4th Cir. 1957); *In re Schoenwald*, 964 F.2d 1122, 22 USPQ 1671 (Fed. Cir. 1992); *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 875, 228 USPQ 90, 99 (Fed. Cir. 1985); *In re Shetty*, 566 F.2d 81, 83, 195 USPQ 753, 754 (CCPA 1977)

[17] Tanuri et al.

SUMMARY

In view of the above, it is respectfully submitted based on the present facts and applicable law that Appellant's invention as claimed is patentable.

It is earnestly requested that the Honorable Board reverse the Examiner's rejection, and that all of the pending claims be allowed.

Please charge any additional fees or credit overpayment to Merchant & Gould Deposit Account No. 13-2725.

Respectfully submitted,

10/21/03
Date

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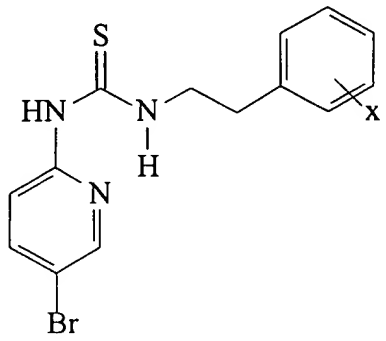
APPENDIX 1

THE CLAIMS ON APPEAL (as finally amended)

23. A method for inhibiting replication of a virus of an HIV strain that is resistant to a chemotherapeutic agent, the method comprising:

contacting the resistant virus with an amount of a compound effective to inhibit replication of the virus,

wherein the compound is of the formula:



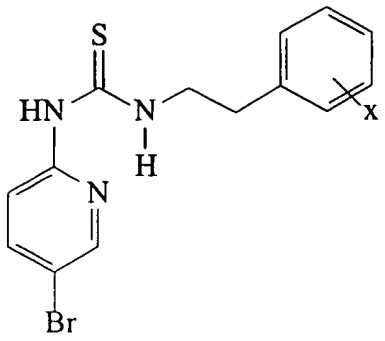
wherein x is: 2,5-OMe or *o*-F.

24. The method of claim 23, wherein the chemotherapeutic agent is Delavirdine, Nevirapine, Efavirenz, Trovirdine, AZT, or MKC-442.

25. A method for inhibiting replication of an HIV having a mutation of an amino acid at position 106 or 183 of reverse transcriptase, the method comprising:

contacting the HIV with an amount of a compound effective to inhibit replication of the HIV,

wherein the compound is of the formula:

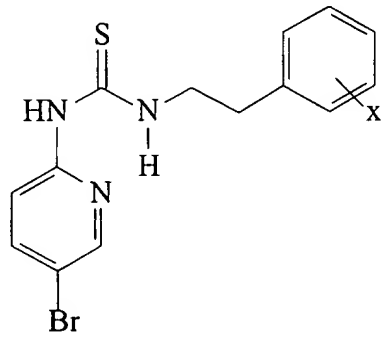


wherein x is: 2,5-OMe or *o*-F.

26. A method for inhibiting replication of an HIV having one or more of the following amino acid substitutions in reverse transcriptase : L100I, K103N, V106A, E138K, Y181C, or Y188H; the method comprising:

contacting the HIV with an amount of a compound effective to inhibit replication of the HIV,

wherein the compound is of the formula:

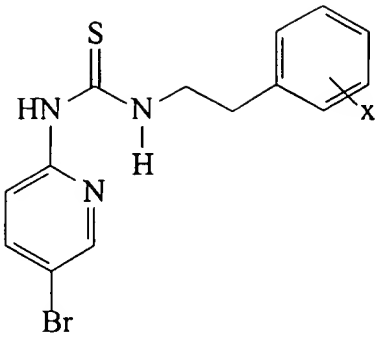


wherein x is: 2,5-OMe or *o*-F.

27. A method for inhibiting replication of a virus of an HIV strain that is resistant to a non-nucleoside inhibitor-resistant strain of HIV; the method comprising

contacting the resistant virus with an amount of a compound effective to inhibit replication of the virus,

wherein the compound is of the formula:

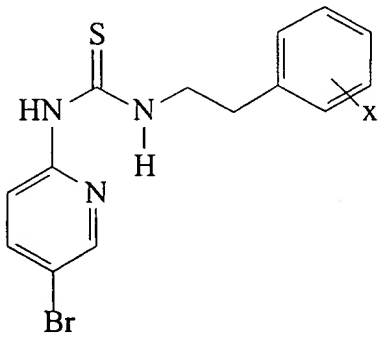


wherein x is: 2,5-OMe or *o*-F.

28. A method of inhibiting replication of a virus of an HIV strain selected from the group consisting of RT-MDR, HIV A17, and HIV A17 variant; the method comprising:

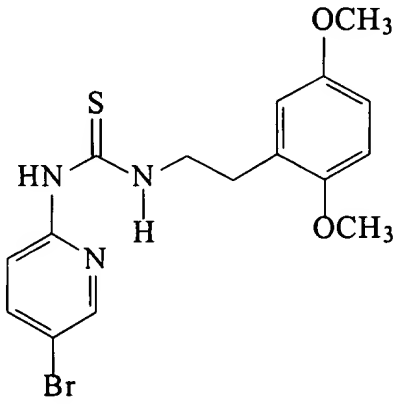
contacting the virus with an amount of a compound effective to inhibit replication of the virus

wherein the compound is of the formula:

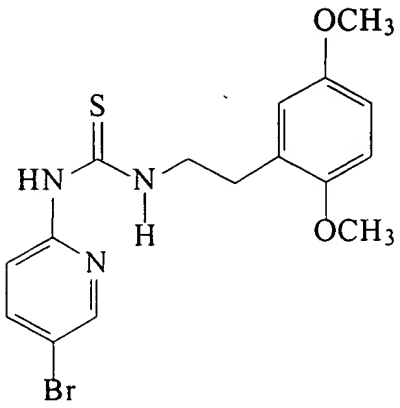


wherein x is: 2,5-OMe or *o*-F.

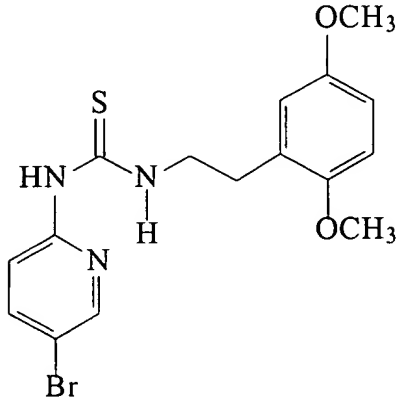
29. The method of claim 23, wherein the compound is



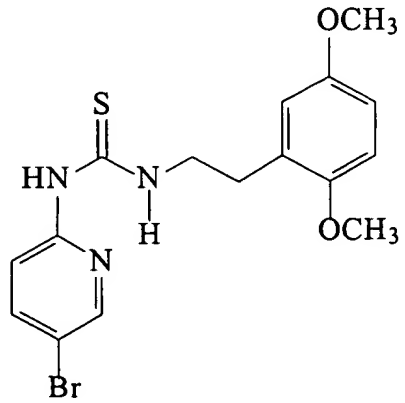
30. The method of claim 25, wherein the compound is



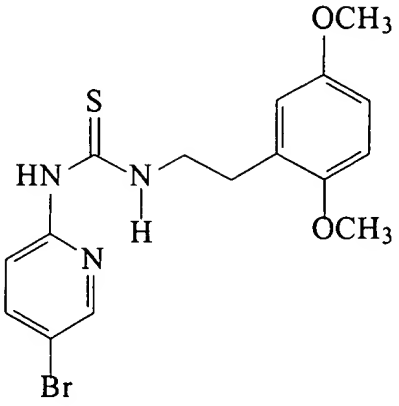
31. The method of claim 26, wherein said compound is



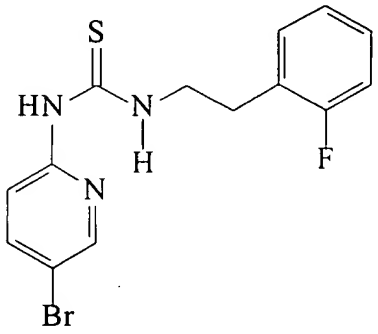
32. The method of claim 27, wherein the compound is



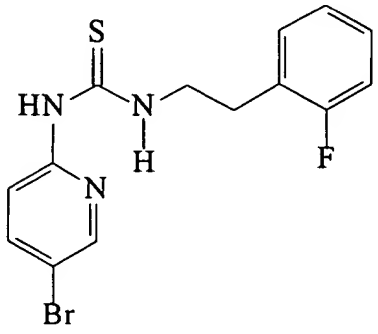
33. The method of claim 28, wherein the compound is



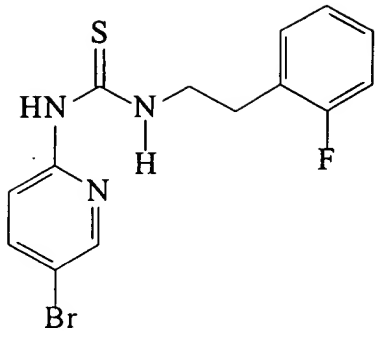
34. The method of claim 23, wherein said compound is



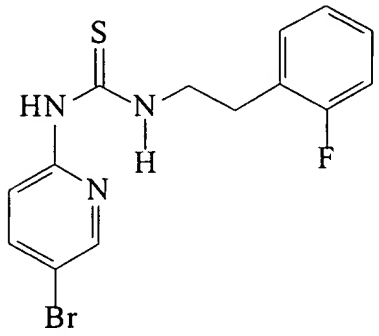
35. The method of claim 25, wherein the compound is



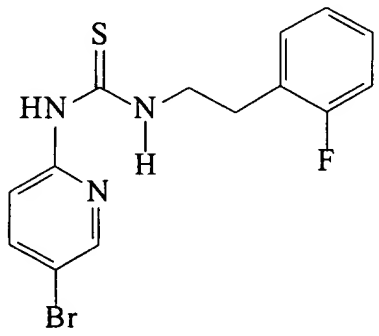
36. The method of claim 26, wherein the compound is



37. The method of claim 27, wherein the compound is



38. The method of claim 28, wherein the compound is



39. The method of claim 23, wherein the replication of the virus is inhibited within a human peripheral blood mononuclear cell.

40. The method of claim 24, wherein the replication of the virus is inhibited within a human peripheral blood mononuclear cell.

41. The method of claim 25, wherein the replication of the HIV is inhibited within a human peripheral blood mononuclear cell.

42. The method of claim 26, wherein the replication of the HIV is inhibited within a human peripheral blood mononuclear cell.

43. The method of claim 27, wherein the replication of the virus is inhibited within a human peripheral blood mononuclear cell.

44. The method of claim 28, wherein the replication of the virus is inhibited within a human peripheral blood mononuclear cell.

APPENDIX 2

OFFICE ACTIONS AND AMENDMENTS/RESPONSES

A. Advisory Action -- mailed October 2, 2003.

B. Amendment under Rule 116 -- mailed August 26, 2003.

C. Final Office Action -- July 1, 2003

APPENDIX 3

REFERENCES RELIED UPON BY THE EXAMINER

A. Lind et al., WO 93/03022.

APPENDIX 4

REFERENCES CITED BY APPELLANTS

A. Rusconi et al., *Antivir. Ther.*, 1(4):211-219, Dec. 1996, at 211 (abstract)

B. Office Action dated September 21, 2001 (Paper No. 14)

C. Masquelier et al., *Antivir. Ther.*, 4(2): 69-77, 1999 (abstract)

D. Shafer et al. "A guide to HIV-1 reverse transcriptase and protease sequencing for drug resistance studies" in *Human Retroviruses and AIDS,* Theoretical Biology and Biophysics. Los Alamos National Laboratories, 2001, pp. 1-51

E. Tanuri et al., *Antimicrobial Agents and Chemotherapy*, 43(2): 253-358, 1999 at 253.

APPENDIX 5

CASES CITED IN THE BRIEF